REMARKS

This communication is being filed in response to the Office Action dated April 6, 2004. Claims 31-42 are pending. Claims 32-34, 36-38, and 40-42 are cancelled herein. Claims 31, 35 and 39 are amended as described hereinabove. Support for the amendments may be found in the specification, *inter alia*, at pp. 15-16. Applicants therefore assert that these amendments do not constitute the addition of new matter.

The Examiner objects to the specification and to Claims 33 and 41 because of the presence of the typographical error "NF-Kß" in place of "NF-κB." In response, Applicants have amended the specification as indicated hereinabove to correct these errors. Claims 33 and 41 have been cancelled, mooting these objections. Applicants therefore respectfully request that the Examiner withdraw the objections to the specification and the claims.

Claims 39-42 are rejected under the second paragraph of 35 U.S.C. § 112 as being indefinite. Claims 31-42 are rejected under both the written description and enablement requirements of the first paragraph of 35 U.S.C. § 112. Claim 39 is rejected under 35 U.S.C. § 102(b) as being anticipated by Liu *et* al. (Human Gene Therapy 1996;7:1719-1726). Applicants respectfully traverse the rejections of the aforementioned claims for the reasons set forth below.

I. The Amended Claims are Definite under the Second Paragraph of 35 U.S.C. § 112

Claims 39-42 are rejected under the second paragraph of 35 U.S.C. § 112 as being indefinite because of insufficient antecedent basis in Claim 39 for the phrase "said ß cell dysfunction."

In response, Applicants hereinabove have amended Claim 39 to indicate that the expression of the inhibitor of IL-1 β activity reduces β cell dysfunction in an individual with a

pancreatic disorder in which said dysfunction results in diabetes. In light of this amendment, Applicants respectfully submit that Claim 39 is definite, and request that the Examiner withdraw the rejection of Claims 39-42 under the second paragraph of 35 U.S.C. § 112.

II. The Amended Claims Satisfy the Written Description Requirement of the First Paragraph of 35 U.S.C. § 112

Claims 31-42 are rejected under the written description requirement of the first paragraph of 35 U.S.C. § 112 because, according to the Examiner, they contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors were in possession of the invention as claimed at the time the application was filed. Specifically, the Examiner asserts that the claims encompass several genuses of IL-1β inhibitors, each genus being of indeterminate size, rather than being limited to particular molecules.

In response, Applicants have amended Claims 31 and 35, which are directed toward methods for reducing β cell dysfunction or preventing Fas-mediated apoptosis of β cells, respectively, and Claim 39, which is directed toward ß cells comprising inhibitors of IL-1ß activity, so that they each now recite specific groups of molecules of defined structure and function. For example, each claim as presently amended is directed, in part, toward nucleic acid molecules that encode the naturally-occurring interleukin-1 receptor antagonist protein (IRAP), a soluble interleukin-1 receptor decoy protein, a soluble type I tumor necrosis factor alpha receptor decoy protein, a human insulin growth factor I (IGF-I) protein, a human insulin-like growth factor II (IGF-II) protein, a signal transducer and activator of transcription 6 (STAT-6) protein, and a nuclear factor of activated T cell (NF-AT) protein. Each of the individual proteins present in these claims are clearly identified and described in the specification as filed. *See* pp. 15-16 of the instant application. In addition, Applicants assert that a representative number of soluble

interleukin-1 receptor decoy proteins to support claims to this genus also have been identified and described in the material incorporated by reference into the instant specification on pp. 15, lines 1-11. As stated in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed.Cir. 1986), "a patent need not teach, and preferably omits, what is well known in the art." On the basis of these amendments, Applicants assert that Claims 31, 35, and 39 satisfy the written description requirement of 35 U.S.C. § 112, and respectfully request the withdrawal of the rejection of Claims 31, 35 and 39 under the first paragraph of 35 U.S.C. § 112. The cancellation of Claims 32-34, 36-38 and 40-42 renders moot the rejection of these claims under 35 U.S.C. § 112.

III. The Claims are Enabled under the first paragraph of 35 U.S.C. § 112

Claims 31-42 are rejected under the first paragraph of 35 U.S.C. § 112 on two grounds. First, the Examiner alleges that the claims in question are not enabled because the specification fails to provide adequate description of a representative number of inhibitors encompassed by the claims. Applicants respectfully suggest that the amendments set forth above to Claims 31, 35 and 39 are sufficient to overcome this basis for an enablement rejection, because the species of IL-1ß inhibitors claimed are now adequately described.

The Examiner also asserts that the specification does not enable any person skilled in the art to make or use the invention commensurate with the full scope of the claims. The Examiner does concede that the specification is enabling for a method of reducing ß cell apoptosis or a method of reducing Fas-mediated ß cell apoptosis in a diabetic individual, said methods comprising transfection into a ß cell isolated from said individual a nucleic acid encoding IRAP or IGF-1 and reimplanting the transfected cell into the donor individual. The Examiner also

concedes that the specification is enabling for a mammalian ß cell comprising a nucleic acid encoding and expressing IRAP or IGF-1. However, the Examiner alleges that the specification is not enabling for claims that ß cell dysfunction in a diabetic individual may be reduced through the reimplantation of ß cells following their *ex vivo* transfection with nucleic acids encoding and expressing IRAP or IGF-1.

In response, Applicants respectfully submit that the teaching of the instant specification does provide adequate guidance to show that ß cell dysfunction and hence a treatment for diabetes results from the claimed procedure. In support of their position, Applicants note that glucose-stimulated insulin secretion was assayed in the transfected ß cells, *see e.g.* specification at pp. 33-34, and that these assays clearly demonstrated that the transfection of IRAP or IGF-1 preserved glucose-stimulated insulin secretion in ß cells after exposure to IL-1ß, *see* specification at pp 36-37 and pp. 43-44. Furthermore, the specification clearly demonstrates that the transfection of IRAP or IGF-1 suppresses IL-1ß-mediated, Fas-triggered apoptosis of ß cells, *see* specification at pp 38-39 and p. 42. Thus, the specification clearly demonstrates that the claimed methods are useful in preventing apoptosis of ß cells and that the transfected cells maintain their capability to sense external glucose, to synthesize insulin and to release insulin under appropriate stimulatory conditions.

The Examiner also expresses concerns that the claimed *ex vivo* treatment approach may be insufficient to treat diabetes in diabetic individuals for the reasons set forth in Levine *et al.* (Mol. Med. Today 5, 165-171). In response, Applicants note that, using the methods described in the instant specification, reimplantation of ß cells into which the IRAP gene has been transfected *ex vivo* does in fact result in long-term maintenance of euglycemia in the NOD mouse, an art-recognized model of type 1 diabetes. Applicants direct the Examiner's attention to the

information provided in the enclosed article by Bertera *et al.* (Bertera S, Alexander AM, Crawford ML, Papworth G, Watkins SC, Robbins PD, Trucco M. Gene Combination Transfer to Block Autoimmune Damage in Transplanted Islets of Langerhans. *Experimental Diabesity Research* 2004;5:201-210), in which euglycemia was achieved in this model for the full 90 day observation period following the adenovirus-mediated transfer of the IRAP gene to islets *ex vivo* followed by their reimplantation into NOD recipients. These studies, which were carried out in accordance with the teachings of the instant specification, provide results that clearly demonstrate the efficacy of the treatment approach described and claimed in the instant application.

In light of the amendments to the claims and the arguments and data provided herein and in the accompanying research article, Applicants respectfully submit that Claims 31, 35, and 39 are fully enabled by the specification, and respectfully request that the rejection of Claims 31, 35 and 39 under the enablement requirement of the first paragraph of 35 U.S.C. § 112 be withdrawn.

IV. The Amended Claims are Not Anticipated under 35 U.S.C. § 102(b)

Claim 39 is rejected under 35 U.S.C. § 102(b) as being anticipated by Liu *et al.* (Human Gene Therapy 1996;7:1719-1726). The Examiner asserts that Liu *et al.* teach a mammalian cell, specifically a human or mouse ß cell, which comprises a vector that expresses the anti-apoptotic gene Bcl-2. The Examiner notes that the specification, at page 18, identifies Bcl-2 as an inhibitor of IL-1ß. Consequently, according to the Examiner, Liu *et al.* anticipates Claim 39, which is directed toward a mammalian ß-cell containing a recombinant nucleic acid molecule which expresses an inhibitor of IL-1 β activity.

In response, Applicants have amended Claim 39 to provide greater specificity to the claimed subject matter. Specifically, Claim 39 is now directed toward

> [a] mammalian ß-cell comprising a recombinant nucleic acid molecule, said nucleic acid molecule comprising and expressing a nucleic acid molecule encoding a protein selected from the group consisting of the naturally-occurring interleukin-1 receptor antagonist protein (IRAP), a soluble interleukin-1 receptor decoy protein, a soluble type I tumor necrosis factor alpha receptor decoy protein, a human insulin growth factor I (IGF-I) protein, a human insulin-like growth factor II (IGF-II) protein, a signal transducer and activator of transcription 6 (STAT-6) protein, and a nuclear factor of activated T cell (NF-AT) protein, wherein the expression of the nucleic acid reduces β cell dysfunction in an individual with a pancreatic disorder in which said dysfunction results in diabetes.

Support for this amendment may be found in the instant specification, *inter alia*, in the first paragraph on page 15, first full paragraph on page 16, and in the references cited therein, which were incorporated into the application by reference in their entireties, as noted in the last paragraph on page 53. Applicants assert that this amendment therefore does not constitute the introduction of new matter. Because Liu *et al.* do not disclose such nucleic acids, this reference cannot anticipate Claim 39 as presently amended. Applicants therefore respectfully request the withdrawal of the rejection of Claim 39 under 35 U.S.C. § 102(b).

CONCLUSIONS

In light of the amendments and the arguments and data provided herein and in the accompanying research article by Prof. Paul Robbins, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

Applicant respectfully petitions for a three-month extension of time. A check in the amount of $1,065.00 is enclosed, representing the $490.00 fee for a three-month extension of time for a small entity, the $395.00 fee for a Request for Continued Examination, and the $180.00 fee for the submission of an Information Disclosure Statement. Should any fees be required in connection with this filing, the Commissioner is hereby authorized to charge Deposit Account Number 02-4377. Two copies of this communication are enclosed.

Respectfully submitted,

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Enclosures